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**UNITED STATES ENVIRONMENTAL PROTECTION AGENCY**  
WASHINGTON, D.C. 20460



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**OFFICE OF PREVENTION, PESTICIDES  
AND TOXIC SUBSTANCES**

**OPP OFFICIAL RECORD  
HEALTH EFFECTS DIVISION  
SCIENTIFIC DATA REVIEWS  
EPA SERIES 361**

**MEMORANDUM**

**Date:** December 16, 2008

**SUBJECT:** **Sulfosulfuron:** Second Report of the Cancer Assessment Review Committee

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**Petition No.:** N/A

**Regulatory Action:** N/A

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**CAS No.:** 141776-32-1

**MRID No.:** N/A

**40 CFR:** N/A

**FROM:** Jessica Kidwell, Executive Secretary  
Cancer Assessment Review Committee  
Health Effects Division (7509P)

*Jessica Kidwell*

**THROUGH:** Jess Rowland, Co-chair  
Mary Manibusan, Co-chair  
Cancer Assessment Review Committee  
Health Effects Division (7509P)

*Jess Rowland*

**TO:** PV Shah, Toxicologist  
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Vicki Walters, Risk Manager Reviewer  
PM Team 25, Registration Division

The Cancer Assessment Review Committee met on February 27, 2008 to evaluate the carcinogenic potential of Sulfosulfuron. Attached please find the Final Cancer Assessment Document.

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*CANCER ASSESSMENT DOCUMENT*

EVALUATION OF THE CARCINOGENIC POTENTIAL OF  
***SULFOSULFURON***

PC Code: 085601

Final  
December 16, 2008

CANCER ASSESSMENT REVIEW COMMITTEE  
HEALTH EFFECTS DIVISION  
OFFICE OF PESTICIDE PROGRAMS

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DATA PRESENTATION:

PV Shah

PV Shah, Toxicologist

DOCUMENT PREPARATION:

Jessica Kidwell

Jessica Kidwell, Executive Secretary

COMMITTEE MEMBERS IN ATTENDANCE: (Signature indicates concurrence with the assessment unless otherwise noted.)

Gregory Akerman

Greg Akerman

Lori Brunsman, Statistician

Lori Brunsman

William Burnam

Retired

Marion Copley

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Nancy McCarroll

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Jess Rowland

Jess Rowland

Yin-Tak Woo

Jess Rowland for Y.T.W.

NON-COMMITTEE MEMBERS IN ATTENDANCE: (Signature indicates concurrence with the pathology report)

John Pletcher, Consulting Pathologist

See attached sheet

OTHER ATTENDEES: George Ghali (HED/SIMB)

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## DATA PRESENTATION:

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PV Shah, Toxicologist

## DOCUMENT PREPARATION:

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Jessica Kidwell, Executive Secretary

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John Pletcher, Consulting Pathologist



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## EXECUTIVE SUMMARY

On February 27, 2008, the Cancer Assessment Review Committee (CARC) of the Health Effects Division of the Office of Pesticide Programs met to re-evaluate the carcinogenic potential of sulfosulfuron. This is the second time this chemical has been evaluated by the CARC.

In 1998, the CARC classified sulfosulfuron as a "likely human carcinogen". The weight-of-evidence for this classification included the occurrence of rare transitional cell papilloma and carcinoma of the urinary bladder in female rats, rare benign mesenchymal tumors of the urinary bladder in male mice as well as renal adenomas in male and female mice. At that time the Committee recommended that a linear low-dose approach ( $Q_1^*$ ) for human risk characterization and extrapolation of risk should be based on the incidence of benign mesenchymal tumors in male mice. This extrapolation, rather than an MOE approach, was warranted due to lack of data on mode of action (MOA). The Registrant was asked to consult the Agency if they wish to conduct additional studies to support a mode of action (MOA) for the carcinogenicity of sulfosulfuron. Since that time, the registrant Monsanto made a request to the OPP for cancer reclassification of sulfosulfuron based on data submitted for the MOA for bladder tumors and a re-evaluation of the kidney tumors.

Based on the re-evaluation, the Committee considered the following for a weight-of-evidence determination on the carcinogenic potential of sulfosulfuron:

### Carcinogenicity

#### Rats

- Urinary Bladder Tumors:* At 5,000 ppm, a urinary bladder transitional cell papilloma and carcinoma were each observed in one female rat (2 different animals, each 1 out of 60 animals; not statistically significant). These tumors were not observed in females at lower doses or at the highest dose tested (HDT) of 20,000 ppm, nor in male rats at any dose level. The incidence of papilloma at 5000 ppm (2%) was within the historical control range of the testing laboratory, however the incidence of carcinoma at 5000 ppm was outside the historical control value (0%). The animals that had transitional cell tumors also had calculus formation and related urinary bladder pathology (epithelial hyperplasia). In spite of the lack of dose-response and the low incidence, the CARC concurred with the previous CARC's decision that these urinary bladder tumors are treatment-related since this is a rare tumor, the urinary tract is the target organ, and precursor lesions for the MOA for urinary bladder tumors were noted.
- Adequacy of Dosing:* In males, 5000 ppm was considered to be adequate for assessing the carcinogenic potential of sulfosulfuron based on the abnormal crystals in the urine and slightly increased incidences of kidney and urinary bladder calculi and related lesions (dilatation of the renal pelvis and bladder, urinary bladder epithelial hyperplasia) as well

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as the increased incidence of mineralization of the heart, lung, pancreas and skeletal muscle. The intended high dose of 20,000 ppm, discontinued at day 259, was considered excessive due to high mortality secondary to urolithiasis-related pathology.

In females, dosing at 5000 ppm was considered adequate for assessing the carcinogenic potential of sulfosulfuron. At 5000 ppm (high-mid dose), increased incidences of abnormal urinary crystals, and slightly increased incidences of renal pelvic epithelial hyperplasia and gastric pyloric lesions were observed. The incidence of grossly visible calculi was also increased. At 20,000 ppm (highest dose tested), toxicity to the urinary tract was pronounced. Slightly increased mortality, decreased body weight/weight gain, emaciated appearance, slightly increased BUN, systemic mineralization, fibrous osteodystrophy of the femur and sternum and parathyroid hyperplasia were also observed. Some Committee members considered this dose excessive because mineralization in many organs, may have compromised normal physiological function.

### *Mouse*

- *Urinary Bladder Tumors:* The incidences of benign mesenchymal tumors of the urinary bladder in male mice for average daily doses of 0, 30, 700, 3000, and 7000 ppm, respectively, were:

Benign            0/45, 0/46, 0/48, 1/47 (2%), 5/44 (11%)

There was a significant increasing trend (at  $p < 0.01$ ) and a significant difference in the pair-wise comparison of the high dose group compared to the control (at  $p < 0.05$ ) for benign mesenchymal tumors of the urinary bladder. The incidence at the high dose (11%) also exceeded the historical control data from the testing lab (0-2%). The CARC concurred with the 1998 CARC decision that these tumors were treatment-related since they exceeded the concurrent control and historical control data from the testing laboratory, the urinary tract was the primary target organ of sulfosulfuron, and precursor lesions for the MOA for urinary bladder tumors were noted.

- *Kidney Tumors:* Kidney tubule adenomas were found in one male and one female mouse administered the highest concentration of sulfosulfuron in the diet (7000 ppm). A re-evaluation of the histopathology findings from the chronic mouse study was performed by Dr. Gordon Hard, an international expert in the field of mouse kidney tumors. It was concluded that the renal tubules failed to show any evidence of treatment-related cellular injury or death, increased mitotic activity, or increased nuclear size. Also, there was no incidence of compound-induced hyperplasia. Chronic progressive nephropathy (CPN) was observed with almost 100% occurrence in the four treatment groups, including controls. The severity of these lesions was comparable among groups. Therefore, this evaluation indicates that the kidney adenomas were not treatment-related.

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- *Adequacy of Dosing:* The highest dose tested (7000 ppm) was considered adequate for assessing the carcinogenic potential of sulfosulfuron. In males, urinary tract pathology secondary to treatment-related urolithiasis were observed at 3000 and 7000 ppm and included mucosal epithelial hyperplasia, chronic inflammation and ulceration. Although no treatment-related toxicity was seen in females at this dose (7000 ppm), since it is the limit-dose for carcinogenicity testing, dosing was considered to be adequate for assessing carcinogenicity.

### Mutagenicity

- There is no concern for mutagenicity.

### Structure Activity Relationship

- Sulfosulfuron is a sulfonylurea herbicide and is structurally related to several other sulfonylurea compounds. As a group, these compounds do not show evidence of carcinogenicity among those that have been classified. Some sulfonamide drugs which are carbonic anhydrase inhibitors have been shown to cause urinary calculus formation and bladder tumors in rodents.

A Derek Analysis was also performed for sulfosulfuron. The Derek analysis for sulfosulfuron reported an alert for bladder urothelial hyperplasia based on the aryl sulphonamide portion of the parent structure. The toxicophore for this alert has been based on the chemical structures of well-known sulphonamide-type carbonic anhydrase inhibitors and some consideration of potential precursors (hydrolysis of N-acetyl groups to the free amine). In addition to the aryl sulphonamide alert, a carcinogenic alert was reported based on the bladder urothelial hyperplasia being associated with the formation of tumors of the bladder. This alert is based on the substituted pyrimidine or purine structure. Pyrimidine derivatives have been shown to have carcinogenic potential include uracil and thymine, which included bladder carcinogenesis in rats and/or mice via calculi formation. Urinary calculi are formed when the urine becomes oversaturated with a compound. Large calculi then damage the urinary bladder epithelium mechanically and increase DNA synthesis in the cells resulting in tumor formation. In conclusion, these structural alerts correspond accurately with the results of the empirical data for potential bladder carcinogenicity based on a non-genotoxic mode of action based on a high dose phenomenon that includes formation of urinary calculi causing damage to the urinary bladder epithelium which increases cellular proliferation and hyperplasia which lead to bladder tumor formation.

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**Mode of Action**

- The series of events leading to urinary bladder tumors (mesenchymal and transitional cell) are initiated by the formation of crystals in urine and the aggregation (accretion) of crystals to form calculi or stones, which induce a hyperplastic (preneoplastic) response in the urinary bladder epithelium. Urinary bladder epithelial hyperplasia is a regenerative response resulting from irritation and inflammation caused by an abrasive action of calculi on the urinary bladder epithelium. Urinary bladder lesions that precede or accompany epithelial hyperplasia may include inflammation (acute or chronic), ulceration, and necrosis. Crystal formation in the absence of calculi is not associated with hyperplasia or urinary bladder tumors; therefore, the formation of urinary bladder calculi is the prerequisite for subsequent hyperplasia and neoplasia. The requirement for calculi formation also supports high-dose threshold phenomenon for the development of urinary bladder tumors, i.e., tumors do not develop at doses too low to produce calculi.

**Classification and Quantification of Carcinogenic Potential**

In accordance with EPA's *Final Guidelines for Carcinogen Risk Assessment (March 2005)*, the CARC classified Sulfosulfuron as "Not Likely to be Carcinogenic to Humans" at doses that do not cause crystals with subsequent calculi formation resulting in cellular damage of the urinary tract. This classification was based on urinary bladder tumors seen in female rats and male mice. Crystal formation in the absence of calculi is not associated with hyperplasia or urinary bladder tumors; therefore, the formation of urinary bladder calculi is the prerequisite for subsequent hyperplasia and neoplasia. The requirement for calculi formation also supports a high-dose threshold phenomenon for the development of urinary bladder tumors, i.e., tumors do not develop at doses too low to produce calculi. There is no concern for mutagenicity.

A quantified approach to cancer risk assessment is not required.

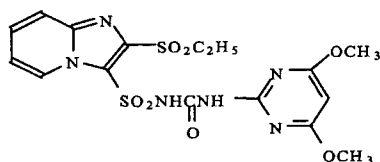
## I. INTRODUCTION

On February 27, 2008, the Cancer Assessment Review Committee (CARC) of the Health Effects Division of the Office of Pesticide Programs met to re-evaluate the carcinogenic potential of Sulfosulfuron. This is the second time this chemical has been evaluated by the CARC.

[This report supercedes the first CARC report dated 10/16/98 (HED Doc. No. 012915).]

## II. BACKGROUND INFORMATION

Sulfosulfuron (MON 31500) is a sulfonylurea herbicide. It is a selective pre- and post-emergent herbicide for the control of various annual grasses and broadleaf weeds in winter and spring wheat and non-food crops and a variety of other uses including ornamentals, roadsides, airports, lumber yards, recreational areas, parks, golf courses, residential areas (lawns), industrial rights of way, etc. Sulfonylurea herbicides disrupt amino acid biosynthesis in susceptible plants by binding to the acetolactate synthase (ALS) enzyme. Its chemical name is 1-(4,6-dimethoxypyrimidin-2-yl)-3-[(2-ethylsulfonylimidazo{1,2-a}pyridin-3-yl)sulfonyl]urea. The PC Code No. is 085603. The chemical structure is shown below in Figure 1.



**Figure 1: Sulfosulfuron**

In 1998, the Cancer Assessment Review Committee of the Health Effects Division of the Office of Pesticide Programs met to evaluate the carcinogenic potential of sulfosulfuron (HED Doc. No. 012915). The CARC classified sulfosulfuron as a “likely human carcinogen”. The weight-of-evidence for this classification was as follows:

- (i) occurrence of rare transitional cell papilloma and carcinoma of the urinary bladder in female rats;
- (ii) occurrence of rare mesenchymal tumors of the urinary bladder in male as well as renal adenomas in male and female mice;
- (iii) can not discount the relevancy of the observed tumors to human exposure.

At that time the Committee recommended that a linear low-dose approach ( $Q_1^*$ ) for human risk characterization and extrapolation of risk should be based on the incidence of benign mesenchymal tumors in male mice. Although all three tumor types were considered to be

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biologically significant, the mesenchymal tumors were selected for extrapolation since this is the only tumor type that exhibited statistical (positive trend and pair-wise) significance. This extrapolation, rather than an MOE approach, was warranted due to lack of data on mode of action (MOA). The Registrant was asked to consult the Agency if they wish to conduct additional studies to support a mode of action (MOA) for the carcinogenicity of sulfosulfuron.

Since that time, the registrant Monsanto made a request to the OPP for cancer reclassification of sulfosulfuron based on data submitted for the MOA for bladder tumors and an expert re-evaluation of the kidney tumors. Monsanto submitted following documents:

1. Expert report on renal histopathological changes in a mouse study with MON 37500: Addendum to Oncogenicity study of MON 37500 Administered in Diet to CD-1 mice for 18 months (MRID 45079601);
2. Determination of Sulfosulfuron Concentration in rat bladder calculi (Addendum to: Combined Chronic Toxicity/Oncogenicity study of MON 37500 Administered in the diet to Sprague-Dawley rats, MRID 45079602);
3. Studies on the relevance of Kidney and Urinary bladder tumors in chronic studies with sulfosulfuron (MRID 45362801);
4. Special mechanistic study: urinary bladder parameters (MRID 45643601).

The CARC met on February 27, 2008 to re-evaluate the carcinogenic potential of sulfosulfuron according to the new 2005 carcinogenicity guidelines in light of the new data submitted.

### III. EVALUATION OF CARCINOGENICITY STUDIES

#### 1. Combined Chronic Toxicity/Carcinogenicity Study in Rats

Reference: Naylor, M.W. and Ruecker, F.A. (1997) Combined Chronic Toxicity/Oncogenicity Study of MON 37500 Administered in the Diet to Sprague-Dawley Rats. Monsanto Study No. ML-94-118. Laboratory Project No. EHL 94051. March 14, 1997. MRID 44295759. Unpublished study.

##### A. Experimental Design

Sulfosulfuron (98.4% a.i.) was continuously administered to 50 Sprague-Dawley (CD) rats/sex/dose in the diet at dose levels of 0, 50, 500 and 5000 ppm and to 50 females at 20,000 ppm for 22 months. Fifty males were also assigned at 20,000 ppm, but surviving animals were sacrificed on day 259 due to excessive mortality from the effects of urolithiasis. An additional 10 rats/sex/dose (except 20,000 ppm males) were assigned to an interim (12-month) sacrifice.

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Average daily intake of test material was 0, 2.4, 24.4 or 244.2 mg/kg/day for males up to 5000 ppm (1,178.3 for males at 20,000 ppm through day 259) and 3.1, 30.4, 314.1 or 1,296.5 mg/kg/day for females.

#### B. Discussion of Tumor Data

*Urinary Bladder Transitional Cell Tumors:* At 5,000 ppm, a urinary bladder transitional cell adenoma and carcinoma were each observed in one female (2 different animals, each 1 out of 60 animals; not statistically significant) (Table 1). These tumors were not observed in females at lower doses or at the highest dose tested (HDT) of 20,000 ppm, nor in males at any dose level.

**Table 1. Sprague Dawley Rat: Female Urinary Bladder Transitional Cell Tumor Rates<sup>1</sup>**

Transitional Cell Bladder Tumors	Dose				20,000 ppm
	0 ppm	50 ppm	500 ppm	5000 ppm	
	0 mg/kg/day	3.1 mg/kg/day	30.4 mg/kg/day	314.1 mg/kg/day	1296.5 mg/kg/day
Papilloma	0/60	0/59	0/60	1/60 (2%)	0/57
Carcinoma	0/60	0/59	0/60	1/60 (2%)	0/57

<sup>1</sup> Data extracted from Table 23, Appendix 2 and Table 12, Appendix 7 of study report. The denominator includes animals assigned to the interim sacrifice groups.

\*= Statistically significant at  $p < 0.05$ ; \*\*= statistically significant at  $p < 0.01$

Historical control data from the testing laboratory for the incidence of urinary bladder transitional cell tumors in Sprague-Dawley CD rats were provided. Data from 16 long-term studies conducted between 1982 and 1992 were available (all animals were from Charles River Portage, MI facility; in the sulfosulfuron study, all animals were from the Raleigh, NC facility). Transitional cell papilloma was observed in 0/808 males and in 1/814 females (mean incidence 0.12%; range 0%-2%). No transitional cell carcinomas were reported.

Historical control data on Sprague-Dawley rats have been published by the supplier, Charles River Laboratories. Animals were supplied by the Portage, MI, Kingston, NY, Lakeview, NJ or Montreal, Canada facilities and data were collected from independent testing laboratories. Among a total of 1,249 female rats from 19 groups in 24-month studies, 1 urinary bladder transitional cell papilloma and 1 carcinoma were observed (mean 0.08% incidence; range 0-1.4%). In male rats (19 groups, 1,250 animals), 1 papilloma (mean incidence 0.08%; range 0-1.4%) and 3 carcinomas (mean incidence 0.24%; range 0%-1.5%) were observed.

### C. Non-neoplastic Lesions

The incidences of selected non-neoplastic lesions in male and female rats are presented in Tables 2 and 3, respectively. The primary target organ of sulfosulfuron was the urinary tract in both males and females.

At 5000 ppm microscopic findings in males included renal calculi; dilatation of the renal pelvis; urinary bladder mucosal epithelial hyperplasia and dilatation; and increased incidence of mineralization in the kidney, heart, lung, pancreas and skeletal muscle. In females, urinary bladder mucosal epithelia hyperplasia, kidney pelvic epithelial hyperplasia, pelvic dilatation, renal calculus, and gastric pyloric erosions were observed. Females at interim sacrifice showed a slightly increased incidence of urinary tract calculi and related lesions.

At 20,000 ppm, gross and microscopic lesions of the urinary tract in both sexes, including kidney or bladder calculi, dilatation, mineralization of renal cortex/medulla, bladder mucosal epithelial hyperplasia, pyelonephritis (females), squamous metaplasia of renal pelvic epithelium (females), increased severity of nephropathy (females), renal suppurative inflammation (females), necrosis of renal papilla (males) and hemorrhage of renal pelvis or bladder (males). In females, parathyroid hyperplasia, fibrous osteodystrophy of the femur and sternum, and mineralization the aorta, cornea, heart, lungs, mesentery, pancreas, skeletal muscle, thyroid and spleen were observed.

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**TABLE 2: SELECTED NON-NEOPLASTIC LESIONS IN MALE RATS FED SULFOSULFURON<sup>a</sup>**

Organ/lesion	0 ppm	50 ppm	500 ppm	5,000 ppm	20,000 ppm
	0 mg/kg/day	2.4 mg/kg/day	24.4 mg/kg/day	244.2 mg/kg/day	1178.3 mg/kg/day
<b><u>Males</u></b>					
<b>Bladder</b> , Mucosal epith. hyperpl.	6/56b	6/59	5/59	9 (15)	14/21 (67)
Dilatation	0/56 (0)	1/59	1/59	3 (5.0)	2/21 (10)
Calculus	0/56	0/56	0/59	0	2/21 (10)
Mineralization	1/56 (1.8)	0/56	0/59	0	4/21 (20)
Hemorrhage	0/56	0/56	0/59	2 (3.3)	3/21 (14)
<b>Kidney</b> , Pelvic calc./microcalc.	0/59	0/59	0/59	2 (3.3)	2/21 (10)
Dilatation, pelvis	8/59 (14)	7/59	7/59	3 (5)	21/21 (100)
Hyperplasia, pelvic epithelium	23/59 (40)	16/59	18/59	23 (38)	15/21 (71)
Mineralization, cortex/medulla	8/59 (14)	5/59	4/59	12 (20)	18/21 (86)
Mineralization, papilla	7/59 (12)	11/59	3/59	6 (10)	6/21 (29)
Necrosis, papilla	1/59 (1.7)	0/59	1/59	1 (1.7)	4/21 (19)
Hemorrhage, pelvis	0/59	0/59	1/59	0	3/21 (14)
<b>Ureter</b> , Dilatation	1/2 (50)	--	0/2	0/2	1/8 (13)
Hyperplasia	1/2 (50)	--	1/2	0/2	4/8 (50)
<b>Heart</b> , Mineralization, myocardium	5 (8.3)	3	3	9 (15)	-- <sup>c,d</sup>
Mineralization, vascular	6 (10)	3	3	10 (17)	--
<b>Lung</b> , Random mineralization	1 (1.7)	0	0	4 (6.7)	--
<b>Pancreas</b> , Vascular mineralization	1/58 (1.7)	1/57	1/59	3/56 (5.4)	--
<b>Skeletal muscle</b> , Mineralization	3 (5.0)	1	4	9 (15)	--
<b>Seminal vesicles</b> , Dilatation	0/57	2/57	0	4 (6.7)	--
Inflammation	2/5 (3.5)	3/57	4	5 (8.3)	--

a Data extracted from Table 19, Appendix 2 and Table 12, Appendix 7, MRID 44295759. N = 60 unless otherwise indicated. Only some ureters with gross findings evaluated microscopically.

b Values in parentheses indicate percent incidence.

c -- No animals were evaluated.

d Data summarized by TB-I from individual animal data, Appendix 7, Table 12, MRID 44295759 (not analyzed statistically).

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**TABLE 3: SELECTED NON-NEOPLASTIC LESIONS IN FEMALE RATS FED SULFOSULFURON<sup>a</sup>**

	0 ppm	50 ppm	500 ppm	5,000 ppm	20,000 ppm
Organ/Lesion	0 mg/kg/day	3.1 mg/kg/day	30.4 mg/kg/day	314.1 mg/kg/day	1296.5 mg/kg/day
<b><u>Females</u></b>					
<b>Bladder</b> , Mucosal epith. hyperpl.	2 (3.3)	2/59	0	3 (5.0)	10/57 (18)*
<b>Kidney</b> , Pelvic epith. hyperplasia	8 (13)	1/10	4	17 (28)	26 (43)**
Calculus/microcalc., pelvis	0	0/10	0	1 (1.7)	13 (22)**
Pelvic dilatation	1	1/10	2	8 (13)	20 (33)**
Pyelonephritis	1 (1.7)	1/10	2	1 (1.7)	7 (12)
Squam. metaplasia, pelvic epith.	0	0/10	0	0	5 (8.3)
Mineralization, cortex/medulla	3 (5.0)	0/10	4	3 (5.0)	17 (28)**
Suppurative inflammation	0	0	0	1 (1.7)	2 (3.3)
<b>Ureter(s)</b> , Dilatation/distension	--	--	--	--	4/7 (57)
Inflammation	--	--	--	--	4/7 (57)
Hyperplasia, mucosal epith.	--	--	--	--	5/7 (71)
Calculi	--	--	--	--	2/7 (29)
Erosion/ulceration	--	--	--	--	1/7 (14)
Squamous metaplasia	--	--	--	--	2/7 (29)
Mineralization	--	--	--	-	1/7 (14)
<b>Aorta</b> , Mineralization	1 (1.7)	--	0	0	10 (17)*
<b>Femur</b> , Fibrous osteodystrophy	1 (1.7)	--	0	0	7 (12)
<b>Sternum</b> , Fibrous osteodystrophy	1 (1.7)	--	0	0	7 (12)
<b>Eye</b> , Corneal mineralization	0/59	--	0/58	1/59 (1.7)	3/55 (6)
<b>Heart</b> , Myocardial mineralization	1 (1.7)	--	0	1 (1.7)	9 (15)*
Vascular mineralization	1 (1.7)	--	0	1 (1.7)	11 (18)**
<b>Lungs</b> , Random mineralization	1 (1.7)	0/10-	0	0	7 (12)

a Data extracted from Table 19, Appendix 2, MRID 44295759. N = 60 unless otherwise indicated.

b Values in parentheses indicate percent incidence.

c -- No animals were evaluated.

\* Statistically significant,  $p \leq 0.05$ ; \*\*  $p \leq 0.01$ . Lesions in ureter and mesentery not analyzed statistically.

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#### D. Adequacy of Dosing for Assessment of Carcinogenic Potential

In male rats, 5000 ppm was considered to be adequate for assessing the carcinogenic potential of sulfosulfuron based on the abnormal crystals in the urine and slightly increased incidences of kidney and urinary bladder calculi and related lesions (dilatation of the renal pelvis and bladder, urinary bladder epithelial hyperplasia) as well as the increased incidence of mineralization of the heart, lung, pancreas and skeletal muscle. The intended high dose of 20,000 ppm, discontinued at day 259, was considered excessive due to high mortality secondary to urolithiasis-related pathology.

In female rats, dosing at 5000 ppm was considered adequate for assessing the carcinogenic potential of sulfosulfuron. At 5000 ppm (high-mid dose), increased incidences of abnormal urinary crystals, and slightly increased incidences of renal pelvic epithelial hyperplasia and gastric pyloric lesions were observed. The incidence of grossly visible calculi was also increased. At 20,000 ppm (highest dose tested), toxicity to the urinary tract was pronounced. Slightly increased mortality, decreased body weight/weight gain, emaciated appearance, slightly increased BUN, systemic mineralization, fibrous osteodystrophy of the femur and sternum and parathyroid hyperplasia were also observed. Some Committee members considered this dose excessive because mineralization in many organs, may have compromised normal physiological function.

#### 2. Carcinogenicity Study in Mice

Reference: Naylor, M.W. and Thake, D.C. 1997. Oncogenicity Study of Sulfosulfuron Administered in Diet to CD-1 Mice for 18 Months. Monsanto Company (CEREGEN) Environmental Health Laboratory. Monsanto Study No. ML-94-119; Laboratory Project No. EHL 94052, MSL 15013. February 19, 1997. MRID 44295755. Unpublished study.

#### A. Experimental Design

Sulfosulfuron (98.4% a.i.) was administered continuously in the diet to 50 CD-1 albino mice/sex/dose at dose levels of 0, 30, 700, 3000 or 7000 ppm. An additional 10 animals/sex/dose were assigned to a 12-month interim sacrifice group. Average daily intake of test material was 0, 4.0, 93.4, 393.6 or 943.5 mg/kg/day for males and 0, 6.5, 153, 634.9 or 1,388.2 mg/kg/day for females.

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**B. Discussion of Survival and Tumor Data***Survival*

The statistical evaluation of mortality indicated no significant incremental changes with increasing doses of sulfosulfuron in male and female mice (Memo, L. Brunsman, 7/23/98, HED Doc. No. 012863).

*Tumors*

*Mesenchymal Urinary Bladder Tumors:* Male mice had a significant increasing trend at  $p < 0.01$ , and a significant difference in the pair-wise comparison of the 7000 ppm dose group with the controls at  $p < 0.05$ , for urinary bladder mesenchymal tumors (Memo, L. Brunsman, 7/23/98, HED Doc. No. 012863). Female mice had no significant increase in compound-related tumors. The statistical analysis of the male mice was based upon the Exact Trend Test and the Fisher's Exact Test for pair-wise comparisons (Table 4).

**Table 4. CD-1 Mice: Male Urinary Bladder Tumor Rates<sup>+</sup> and Exact Trend Test and Fisher's Exact Test Results (p values)**

Mesenchymal Bladder Tumors	Dose				
	0 ppm	30 ppm	700 ppm	3000 ppm	7000 ppm
	0 mg/kg/day	4 mg/kg/day	93.4 mg/kg/day	393.6 mg/kg/day	943.5 mg/kg/day
Incidence	0/45	0/46	0/48	1/47	5 <sup>a</sup> /44
%	0	0	0	2	11
p	<b>0.000**</b>	1.000	1.000	0.511	<b>0.026*</b>

<sup>+</sup>Number of tumor bearing animals/Number of animals examined, excluding those that died or were sacrificed before week 53.

<sup>a</sup>First mesenchymal tumor observed at week 70, dose 7000 ppm.

Note: Significance of trend denoted at control. Significance of pair-wise comparison with control denoted at dose level.

If \*, then  $p < 0.05$ . If \*\*, then  $p < 0.01$ .

*Kidney tubular adenomas:* A kidney adenoma, a tumor that occurs infrequently in CD-1 mice, was found in 1 male and 1 female at 7000 ppm. Since the 1998 CARC meeting, the registrant submitted a re-evaluation of the histopathology findings from the chronic mouse study which was performed by Dr. Gordon Hard, an international expert in the field of mouse kidney tumors (MRID 45362801). Dr. Gordon Hard stated that "careful examination of the renal tubules failed to show any evidence of treatment-related cellular injury or death, increased mitotic activity, or increased nuclear size. Also, there was no incidence of compound-induced hyperplasia. Chronic progressive nephropathy (CPN) was observed with almost 100% occurrence in the four treatment

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groups, including controls. The severity of these lesions was comparable among groups. Taken together and in conjunction with the observation that an adverse response to sulfosulfuron appears to occur only in the event of urinary crystal and then calculus formation and hyperplasia, this evaluation indicates that the adenomas were not a sulfosulfuron-induced event."

#### *Historical Control Data for Urinary Bladder and Kidney Tumors*

Historical control data from the testing laboratory for these tumors in CD-1 mice were available from 16 eighteen-month studies, including this study, initiated between 1984 and 1994. These are the most relevant historical control data. All animals (including the Sulfosulfuron study) were supplied by the Charles River Portage, MI facility. Benign mesenchymal tumors of the urinary bladder were found only in 1/910 males (mean incidence 0.11%; individual study incidence 0%-2%) and 0/911 females. Renal tubular adenomas were reported in a total of 4/956 males in 3 studies (mean incidence 0.42%; range 0%-3%) and in 0/953 females.

Historical control data on the CD-1 mouse have been published by the supplier, Charles River. Twelve groups of animals from 18-month studies conducted at independent contract toxicology laboratories were evaluated between December, 1984 and March, 1991. Animals were supplied by Charles River Facilities in the United Kingdom, Portage, MI, Kingston, NY or Wilmington, MA. Urinary bladder leiomyomas (another term used in this report for benign mesenchymal urinary bladder tumors) were observed in 2/758 males (mean incidence 0.26%; range 0%-2.53%). In 726 females, these tumors were not reported. No benign or malignant neoplasms of the kidney were reported among 770 males or 770 females in 12 groups.

Published studies on urinary bladder benign mesenchymal tumors in Swiss or CD-1 mice were also submitted by the Registrant upon request. The report of Chandra and Frith (1991) describes a low spontaneous incidence of these tumors in 400 male and 400 female control CD-1 mice from 8 studies: 3 female mice in 3 different studies (mean incidence 0.375%; range 0%-2%). These tumors have also been reported following urethral obstruction, implantation of paraffin pellets in the bladder or dietary administration of certain compounds.

#### C. Non-neoplastic Lesions

Selected non-neoplastic lesions in male mice are shown below in Table 5.

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**TABLE 5: SELECTED NON-NEOPLASTIC LESIONS IN MALE MICE FED SULFOSULFURON<sup>1</sup>**

Organ/lesion	0 ppm	30 ppm	700 ppm	3,000 ppm	7,000 ppm
	0 mg/kg/day	4 mg/kg/day	93.4 mg/kg/day	393.6 mg/kg/day	943.5 mg/kg/day
<b><u>Males</u></b>					
<b>Bladder</b> , calculus/microcalculus	1/59	0/59	0/59	4/59	10*
Dilatation	5/59	4/59	3/59	8/59	20**
Hyperplasia, mucosal epithelium	4/59	1/59	2/59	25/59**	41**
Inflammation, chronic					1**
Metaplasia, squamous	2/59	3/59	2/59	23/59**	8*
	0/59	0/59	0/59	1/59	
<b>Kidney</b> , Atrophy	2	0/10	0/59	3/59	11*
Calculus/micro calculus, pelvis	1	0/10	0/59	1/59	3
Dilatation, pelvis	5	0/10	2/59	4/59	27**
Hyperplasia, pelvic epithelium	2	0/10	1/59	1/59	3
Hyperplas./regen., tubular epith.	46/59	8/10	48/59	38/59	46
Mineralization, tubular	38	7/10	39/59	34/59	33
Necrosis, papilla	0/59	0/10	0/59	2/59	2
Mononuclear infiltrate, interstitium/perivascular area	49/59	0/10	51/59	52/59	53
<b>Ureter</b> , calculus/microcalculus	-- <sup>2</sup>	--	--	--	1/1
<b>Heart</b> , Fibrosis, myocardial	8	--	8	7	9
Inflammation, myocardial	3	--	4	1	2
<b>Lung</b> , Mononuclear infiltrate, peribronchiolar/perivascular	21	0/10	19	15	17
<sup>1</sup> Data extracted from Table 18, Appendix 2, MRID 44295755). N = 60 unless otherwise indicated. <sup>2</sup> -- No animals were evaluated. * significantly different from control (0.05); ** significantly different from control (0.01).					

In male mice, the incidence of urinary tract calculus formation and related microscopic lesions of the bladder (including mucosal epithelial hyperplasia, chronic inflammation, ulceration and dilatation) was increased at 3000 and 7000 ppm at study termination. Kidneys also showed effects at 7000 ppm. No treatment-related non-neoplastic lesions were observed in female mice. Grossly visible calculi were observed in many males at 5000 ppm (21/60, bladder) and 7000 ppm (41/60, bladder and 21/60, kidney). Males with benign mesenchymal tumors of the urinary bladder had gross and microscopic lesions of the urinary tract consistent with urolithiasis. Calculi were observed in several animals with bladder tumors (at high dose, 3/5 males with tumors also had urinary calculi). The high-dose female with a benign mesenchymal tumor of the bladder also had calculus formation and related urinary tract pathology, the only female with these lesions. The male with a renal adenoma also had urinary calculus formation and related pathology; however, no kidney or bladder lesions were observed in the female with the renal adenoma. No treatment-related lesions were observed at the interim sacrifice in either males or females.

#### D. Adequacy of Dosing for Assessment of Carcinogenic Potential

The highest dose tested (7000 ppm) was considered adequate for assessing the carcinogenic potential of sulfosulfuron in both male and female CD-1 mice. In males, urinary tract pathology secondary to treatment-related urolithiasis was observed at 3000 and 7000 ppm and included mucosal epithelial hyperplasia, chronic inflammation and ulceration. Although no treatment-related toxicity was seen in females at 7000 ppm, since it is the limit-dose for carcinogenicity testing, dosing was considered to be adequate for assessing carcinogenicity.

### IV. TOXICOLOGY

#### 1. Metabolism

Sulfosulfuron was rapidly excreted (most of the administered dose was excreted within 72 hr post-dosing) (MRID 44295765). Excretion at low doses was primarily via the urine (77%-87% of administered dose at 10 mg/kg), whereas at high dose, excretion was primarily via the feces (55%-63% at 1,000 mg/kg). Urinary elimination was biexponential (initial phase half life 2.2-5.8 hrs and terminal phase half-life 21.4-56.7 hrs); whole-body elimination showed similar kinetics. Absorption was essentially complete at the low dose (10 mg/kg) but limited at the high dose (1,000 mg/kg): it is unclear whether this was a dose-dependent effect or was due to incomplete solubility of the test material in the vehicle at the high dose. There was no significant accumulation of sulfosulfuron or its metabolites in tissues. Biotransformation was limited and most of the administered dose was excreted as unchanged parent compound. The primary routes of metabolism were demethylation and ring-hydroxylation to yield desmethyl and 5-hydroxy Sulfosulfuron metabolites. Low levels of imidazopyridine, pyrimidine and sulfonamide were detected in the urine and/or feces.

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2. Mutagenicity

As shown below in Table 6, sulfosulfuron was shown to be non-mutagenic both *in vivo* and *in vitro* assays submitted to the Agency to satisfy Subdivision F Guidelines. An *in vitro* Chinese hamster lung point mutation assay (under review, 44280201), was positive, but only at precipitating and cytotoxic concentrations ( $\geq 1,000$   $\mu\text{g/mL}$ ). Accordingly, there is no concern for mutagenicity.

**Table 6 Mutagenicity Studies with Sulfosulfuron**

Assay Type	Concentration Tested / Metabolic Activation	Results	MRID No.
Gene Mutation			
Ames: <i>Salmonella</i> - strains TA98, TA100, TA102, TA1535 and TA1537	Tested up to 5,000 $\mu\text{g/plate}$ in the presence or absence of metabolic activation (rat liver S9).	Negative	44295760
<i>In vitro</i> Mammalian Cell Forward Gene Mutation (Chinese hamster ovary cells).	Tested up to 5,000 $\mu\text{g/mL}$ in the presence or absence of metabolic activation (rat liver S9)	Negative	44295761
<i>In vitro</i> Chinese Hamster lung point mutation assay.	Positive but only at cytotoxic and precipitating concentrations ( $\geq 1000$ $\mu\text{g/mL}$ ).	Positive	44280201 (under review)
Chromosomal Aberrations			
<i>In vitro</i> Chromosomal Aberrations (Human lymphocytes).	Tested up to 1,000 $\mu\text{g/mL}$ in the presence or absence of metabolic activation (rat liver S9).	Negative	44295762
<i>In vivo</i> Micronucleus (Mouse).	Tested up to 5,000 mg/kg.	Negative	44295763

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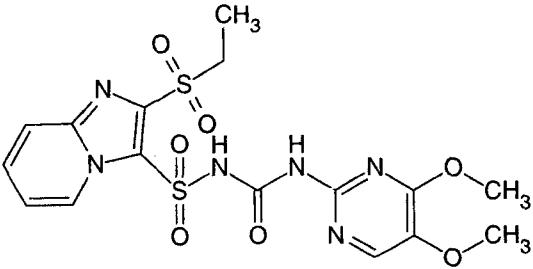
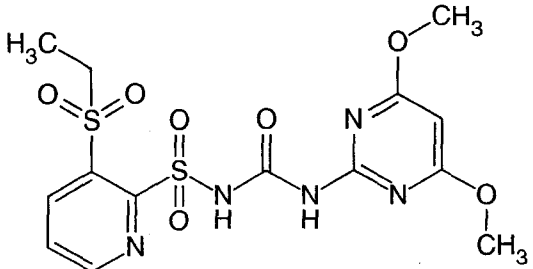
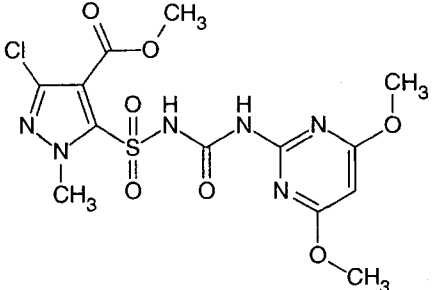
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### 3. Structure Activity Relationship

Sulfosulfuron is a sulfonylurea herbicide. Related sulfuron pesticides and their carcinogenicity classifications are shown below in Figure 2.

**Figure 2. Pesticides Structurally Related to Sulfosulfuron<sup>1</sup>**

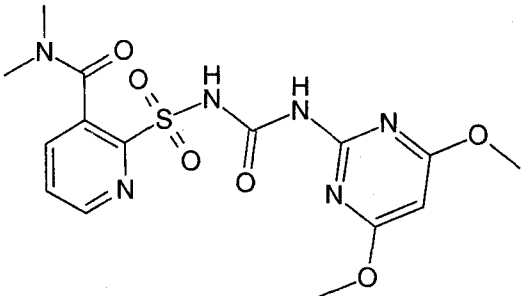
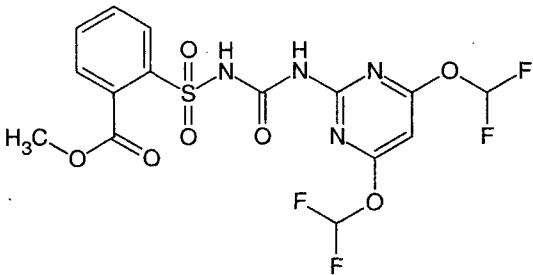
Name	Structure	Current OPP Classification
Sulfosulfuron PC No. 085601		"Not Likely to be Carcinogenic to Humans" at doses that do not cause crystals with subsequent calculi formation resulting in cellular damage of the urinary tract
Rimsulfuron PC No. 129009		Not Likely to be Carcinogenic to Humans
Halosulfuron methyl PC No. 128721		Not Likely to be Carcinogenic to Humans

<sup>1</sup> From OPP's List of "Chemicals Evaluated for Carcinogenic Potential by the Office of Pesticide Programs" dated 9/24/08

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Nicosulfuron PC No. 129008		Group E – Evidence of Non-carcinogenicity for Humans
Primisulfuron methyl PC No. 128973		Group D – Not Classifiable as to Human Carcinogenicity

The above sulfonylurea herbicides classified to-date do not show evidence of carcinogenicity. Of the 6 compounds related to Sulfosulfuron shown here, 2 were classified as “Not Likely to be Carcinogenic to Humans”, one as a Group E (not carcinogenic), and one as D (not classifiable, due to hepatocellular tumors in male mice at an excessive dose).

It was also noted that some sulfonamide drugs have been associated with urolithiasis and bladder tumors in rodents. Acetazolamide and ethylsulfonylnaphthalene-1-sulfonamide are both carbonic anhydrase inhibitors that cause urolithiasis and eventual tumor formation.

A Derek analysis was performed for sulfosulfuron (Derek evaluation July 15, 2008, Memo, Manibusan, M., 8/22/08, TXR No. 0054964). The conclusions are presented below.

**“Bladder Urothelial Hyperplasia Alert:**

The Derek analysis for Sulfosulfuron reported an alert for bladder urothelial hyperplasia based on the fact that this chemical is a member of “Bladder urothelial alert set 1” based on the aryl sulphonamide portion of the parent structure. The toxicophore for this alert has been based on the chemical structures of well-known sulphonamide-type carbonic anhydrase inhibitors and some consideration of potential precursors (hydrolysis of N-acetyl groups to the free amine).

A structurally similar compound to sulfosulfuron, 4-(Ethylsulphonyl) naphthalene-1-sulphonamide (ENS), has been shown to cause bladder urothelial hyperplasia in mice. The formation of bladder carcinoma and stones has also been demonstrated after a minimum of 35 weeks exposure in feed

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studies using 0.01% ENS in the diet. These effects have been related to the increase in urinary pH associated with the action of ENS as a carbonic anhydrase inhibitor, thus indicating a direct relationship with its pharmacologic activity.

#### **Bladder Cancer Alert:**

In addition to the aryl sulphonamide alert, a carcinogenic alert was reported based on the bladder urothelial hyperplasia being associated with the formation of tumors of the bladder. This alert is based on the substituted pyrimidine or purine structure. Pyrimidine derivatives have been shown to have carcinogenic potential include uracil and thymine, which included bladder carcinogenesis in rats and/or mice via calculi formation. Urinary calculi are formed when the urine becomes oversaturated with a compound. Large calculi then damage the urinary bladder epithelium mechanically and increase DNA synthesis in the cells resulting in tumor formation.

#### **Conclusion:**

These structural alerts correspond accurately with the results of the empirical data for potential bladder carcinogenicity based on a non-genotoxic mode of action based on a high dose phenomenon that includes formation of urinary calculi causing damage to the urinary bladder epithelium which increases cellular proliferation and hyperplasia which lead to bladder tumor formation."

#### 4. Subchronic and Chronic Toxicity

##### a. Subchronic Toxicity Studies:

##### Rat

In a subchronic toxicity study (MRID 44295750), MON 37500 (tech., 98.9% a.i.) was administered to 10 male and 20 female Sprague-Dawley rats/dose in the diet at dose levels of 0, 20, 200, 2,000, 6,000 or 20,000 ppm (equivalent to average daily intake of 0, 1.2, 12.1, 123.2, 370.3 or 1,277.5 mg/kg/day, males and 0, 1.5, 14.6, 144.3, 447.5 or 1,489.1 mg/kg/day, females). Ten of the females/dose were mated 1:1 at week 10 with males of the same dose group for up to 7 days in a 1-generation range-finding study. Reproductive and litter parameters were evaluated through lactation day 4.

At 20,000 ppm, mean body weight gain in males was statistically significantly lower than controls at termination (-18%; -28% by comparing gain calculated as percent of initial body weight). Body weight was also lower (-9.4%; not significant). Gain in pregnant females was less than controls (-26%; significant negative trend). When 1 dam with a dead litter was excluded, gain was -15% (not analyzed statistically). In females, a possible increase in incidence of gross and microscopic renal lesions associated with renal calculi (calculus, dilated pelvis, pyelonephritis, hyperplasia of pelvic epithelium, necrotic calcified debris; 2/10 affected) and urinary bladder mucosal epithelial hyperplasia (1/10) was observed. One male had renal calculi and bladder hyperplasia. No treatment-related effects on clinical observations, non-pregnant female body weight, food consumption, ophthalmology, hematology, clinical chemistry parameters, or reproductive/litter parameters were observed. The systemic toxicity

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LOEL is 20,000 ppm (1,277.5 mg/kg/day), based on decreased body weight/weight gain in males, possible decreased weight gain in pregnant females during gestation days 14-21, and possibly renal lesions related to formation of calculi. The NOEL is 6,000 ppm (370.3 mg/kg/day).

This subchronic toxicity study is classified Acceptable and satisfies the guideline requirement for a subchronic oral study (82-1a) in the rat. (The reproductive component of this study is not classified because it was conducted solely as a range-finding study for a later 2-generation reproduction study.)

## Dog

In a subchronic toxicity study (MRID 44295751) MON 37500 (98.4% a.i.) was administered to 50 beagle dogs (5 Males/ 5 Females/dose) by gelatin capsule at dose levels of (0, 30, 100, 300 and 1,000 mg/kg/day) for 90 days. Controls received empty gelatin capsules.

MON 37500's toxic effects were expressed primarily in the urinary tract and appeared to be secondary to formation of urinary calculi at 300 and 1000 mg/kg/day. Abnormal crystals (unidentified) were observed in the urine at day 45 at 300 and 1,000 mg/kg/day (males, 1 and 2, respectively; females, 3 and 2, respectively) and in females at study termination (3 at 300 mg/kg/day and 4 at 1,000 mg/kg/day). Hemorrhage, ulceration, inflammation, and/or mucosal epithelial hyperplasia in the urinary bladder were observed in one female in the 1000 mg/kg/day dose group and one in the 300 mg/kg/day dose group. Two males at 1000 mg/kg/day also showed treatment-related effects. One high dose male was sacrificed due to advanced urolithiasis and associated complications throughout the urinary tract, which included glomerulonephritis, degeneration of renal tubular epithelium, suppurative inflammation of the renal pelvis, arteritis/periarteritis, congestion, tubular protein accumulation and fibrin deposition in the capsular/pericapsular areas. Hemorrhage, erosions and ulcerations with acute inflammation, and degeneration of the tunica muscularis were also observed in the urinary bladder. Inflammation, edema and hemorrhage of periureteral tissue were associated with ureter damage. Inflammation and epithelial necrosis occurred in the urethra. Hemorrhage, acute inflammation and vasculitis/perivasculitis were noted in the prostate gland; the relationship of these lesions to treatment was unclear. The investigators concluded that necrosis of thymic lymphocytes in this male was probably due to release of adrenal cortical hormones subsequent to stress. A second male dog had bladder lesions of acute inflammation, erosions/ulcerations and edema. There were no differences in clinical signs, body weight/weight gain, food consumption, ophthalmologic results or hematology and clinical chemistry parameters related to administration of the MON 37500. The systemic toxicity LOEL is 300 mg/kg/day, based on lesions in the urinary bladder in females occurring subsequent to urinary crystal formation/urolithiasis and on abnormal urinary crystals in males and females. The NOEL for systemic toxicity is 100 mg/kg/day.

This subchronic toxicity study in dogs is classified acceptable and satisfies the guideline requirement for a subchronic oral study (82-1b) in Dogs.

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b. Chronic Toxicity Studies:*Rat*

In a combined carcinogenicity/chronic toxicity study (MRID 44295759), MON 37500 (tech., 98.4% a.i.) was administered to 60 Sprague-Dawley rats/sex/dose in the diet at dose levels of 0, 50, 500, 5,000 ppm and to 60 females at 20,000 ppm for 22 months. Surviving males at 20,000 ppm were sacrificed on day 259 due to excessive mortality (individual animal data only were provided for these males). Ten rats/sex/dose were sacrificed at 12 months. Average daily intake of test material was 0, 2.4, 24.4 or 244.2 mg/kg/day (males up to 5,000 ppm; 1,178.3 mg/kg/day, males at 20,000 ppm until day 259) and 3.1, 30.4, 314.1 or 1,296.5 mg/kg/day (females).

At 5,000 ppm, increased incidence/severity of abnormal crystals in the urine (both sexes, 70-100% affected vs. 10-40%, controls); slight, possibly treatment-related decrease in serum albumin in males (-20%); gross lesions of the urinary tract in females (calculi of kidney/bladder, dilatation of renal pelvis, 5 to 8.3% vs. 0-1.7%, controls) were observed. Microscopic findings in males included renal/urinary bladder calculi (3.3% and 5% vs. 0%, controls); dilatation of the renal pelvis (20% vs. 14%, controls); urinary bladder mucosal epithelial hyperplasia and dilatation (5% and 15% vs. 0% and 11%, controls); and increased incidence of mineralization in the heart, lung, pancreas and skeletal muscle (3.3% to 17% vs. 0 to 10%). In females, kidney pelvic epithelial hyperplasia (28% vs. 13%, controls), pelvic dilatation (13% vs. 0%), renal calculus (1.7% vs. 0%) and gastric pyloric erosions (10% vs. 1.7%) were observed. Females at interim sacrifice showed a slightly increased incidence of urinary tract calculi and related lesions.

At 20,000 ppm, the following were observed: decreased survival in males (-33%, day 259) and possibly in females (-16%, termination); increased occurrence of blood-colored urine in males (37%, beginning on day 51) and intraabdominal swelling (25%, day 135); decreased body weight/weight gain (-9%/-12% by sacrifice in males, up to -12%/-19%, days 51 to 485 in females); possible increased BUN at all time points in females (+20% to +60%); emaciated appearance in females (22% vs. 5%, controls); gross and microscopic lesions of the urinary tract in both sexes, including kidney or bladder calculi, dilatation, mineralization of renal cortex/medulla, bladder mucosal epithelial hyperplasia, pyelonephritis (females), squamous metaplasia of renal pelvic epithelium (females), increased severity of nephropathy (females), renal suppurative inflammation (females), necrosis of renal papilla (males) and hemorrhage of renal pelvis or bladder (males). In females, parathyroid hyperplasia (9% vs. 0%, controls), fibrous osteodystrophy of the femur and sternum (12% vs. 0%), and mineralization the aorta, cornea, heart, lungs, mesentery, pancreas, skeletal muscle, thyroid and spleen (3.7 to 18% vs. 0 to 1.7%, controls) were observed. The LOEL is 5,000 ppm (244.2 mg/kg/day), based on increased incidence of urinary tract gross/microscopic lesions, mineralization in several tissues (males), abnormal urine crystals and possibly decreased albumin (males, termination). The NOEL is 500 ppm (24.4 mg/kg/day).

This study in the rat is classified Acceptable and satisfies the guideline requirement for a carcinogenicity/chronic toxicity study (83-5) in rodents.

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*Mouse*

In a carcinogenicity study (MRID 44295755), MON 37500 (98.4% a.i.) was continuously administered to 60 CD-1 albino mice/sex/dose as a dietary admixture at dose levels of 0, 30, 700, 3000 or 7000 ppm (0, 4.0, 93.4, 393.6 or 943.5 mg/kg/day to males or 0, 6.5, 153.0, 634.9 and 1388.2 mg/kg/day to females) for 18 months. Ten animals/sex/dose were sacrificed at month 12 for hematology, limited serum chemistry analyses and gross/microscopic pathology.

At 3,000 ppm, increased incidence of calculus in the urinary bladder (34% vs. 5%, controls) and microscopic lesions of the bladder caused by calculus formation (mucosal epithelial hyperplasia, 42% vs. 6.8%, controls; chronic inflammation, 39% vs. 3.4%; and ulceration, 5.1% vs. 0%) were reported in males. At 7,000 ppm in males, clinical signs of toxicity (urine-stained fur, intraabdominal swelling and abnormal penile erection; 6-12 affected animals vs. 1-2, controls), dilatation of the renal pelvis (45% vs. 8.3%), dilatation of the bladder (13.3% vs. 0%) were also observed. There were no treatment-related effects on survival, body weight, food consumption or hematology parameters in males and no treatment-related effects were reported in females at any dose tested. The LOEL is 3,000 ppm (393.6 mg/kg/day), based on gross and microscopic effects related to urinary calculus formation in the urinary bladder of males. The NOEL is 700 ppm (93.4 mg/kg/day).

This carcinogenicity study in the CD-1 mice is acceptable and does satisfy the guideline requirement for a carcinogenicity study (83-2(b)) in mice.

*Dog*

In a chronic toxicity study (MRID 44295754) MON 37500 (tech., 98.5% a.i.) was administered to 5 beagle dogs/sex/dose by gelatin capsule at dose levels of 0, 5, 20, 100 or 500 mg/kg/day, 5 days/week) for 1 year. Controls received empty gelatin capsules.

At 500 mg/kg/day, abnormal urinary crystals were reported at 6 months in 1 male, which also developed urinary tract calculi and hemorrhage and thickened/irregular mucosa of the urinary bladder. Two males (including the above male) had yellow crystals in the urine on a total of 5 occasions in cageside observations. There were no compound related effects on mortality, clinical signs, body weight, food consumption, hematology, clinical chemistry, ophthalmology, or organ weights at any dose level. No treatment-related effects were observed in females. The LOEL is 500 mg/kg/day, based on the presence of abnormal urinary crystals and bladder pathology secondary to formation of urinary tract calculi in males. The NOEL is 100 mg/kg/day.

This chronic toxicity study is acceptable and satisfies the guideline requirement for a chronic oral study (83-1(b)) in the dog.

## 5. Mode of Action Analysis for Urinary Bladder Tumors

### **Introduction**

Carcinogenicity studies have been conducted with Sulfosulfuron in mice (CD-1 albino) and rats (Sprague-Dawley). A urinary bladder transitional cell papilloma was observed in one female rat and a urinary bladder transitional cell carcinoma was observed in another female rat administered sulfosulfuron in the diet at 5000 ppm (average dose, 314 mg/kg bw/day). The papilloma was found in an animal sacrificed at study termination (22 months) and the carcinoma was found in an animal found dead on day 95 of the study; both animals had urinary tract calculi. No urinary tract tumors were found in control male rats or in female rats administered the higher dietary concentration of 20,000 ppm (1297 mg/kg bw/day), which was considered to be excessive. In an 18-month carcinogenicity study, benign submucosal mesenchymal tumors were observed in the urinary bladder of 5/44 male mice administered sulfosulfuron at a dietary concentration of 7000 ppm (944 mg/kg bw/day) and in 1/47 administered 3000 ppm (394 mg/kg bw/day). No mesenchymal tumors developed in control male mice. Additional information has been submitted by the registrant to support a mode of action for the urinary bladder tumors with a request to the CARC to review this data and to reconsider the cancer classification of sulfosulfuron based on this information.

1. Hard, G. 1999. Expert Report on Renal Histopathologic Changes in a Mouse Study with MON 37500 (Sulfosulfuron): Addendum to Oncogenicity Study of MON 37500 Administered in Diet to CD-1 Mice for 18 Months. Dr. Gordon Hard, 9 Brundige Dr. Goldens Bridge, NY 10526, Project No. RD. No. 1503. August 4, 1999. MRID 45079601. Unpublished.
2. Dubelman, S. 2000. Determination of Sulfosulfuron Concentration in Rat Bladder Calculi (Addendum to: Combined Chronic Toxicity/Oncogenicity Study of MON 37500 Administered in the Diet to Sprague-Dawley Rats). Monsanto Company, Agricultural Regulatory Group, Environmental Science Technology Center, St. Louis, MO. March 2000. MRID 4507962. Unpublished.
3. Healy, C. 2001. Studies on the Relevance of Kidney and Urinary Bladder Tumors in Chronic Studies with Sulfosulfuron. Project No. R.D. No. 1536. March 21, 2001. MRID 45362801. Unpublished.
4. Cohen, S. And L. Arnold. 2001. Effects of dietary sulfosulfuron on urinary parameters and the bladder in male Sprague-Dawley rats. University of Nebraska Medical Center, Department of Pathology and Microbiology, Omaha, NE. Report No. 080100. March 5, 2001. MRID 45643601. Unpublished.

### **URINARY BLADDER CARCINOGENESIS**

#### ***Summary description of hypothesized mode of action for sulfosulfuron***

The key events in the mode of action of urinary bladder carcinogenesis are presented in Table 7. The series of events leading to urinary bladder tumors (mesenchymal and transitional cell) are initiated by the formation of crystals in urine and the aggregation (accretion) of crystals to form calculi or stones, which induce a hyperplastic (preneoplastic) response in the urinary bladder epithelium. Urinary bladder epithelial hyperplasia is a regenerative response resulting from irritation and inflammation caused by an abrasive action of calculi on the urinary bladder epithelium. Urinary bladder lesions that precede or accompany epithelial hyperplasia may include

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inflammation (acute or chronic), ulceration, and necrosis. Crystal formation in the absence of calculi is not associated with hyperplasia or urinary bladder tumors; therefore, the formation of urinary bladder calculi is the prerequisite for subsequent hyperplasia and neoplasia. The requirement for calculi formation also supports high-dose threshold phenomenon for the development of urinary bladder tumors, i.e., tumors do not develop at doses too low to produce calculi.

<b>TABLE 7. Key events for the mode of action of urinary bladder carcinogenesis in sulfosulfuron-treated animals</b>				
<b>Event</b>	<b>Relationship</b>	<b>Weight-of-evidence</b>	<b>Specificity</b>	<b>Comments</b>
1. Formation of crystals in the urine	Causal	Strong	High	Crystals were found consistently in the urine in studies with multiple species (rats, mice, and dogs) administered high doses of sulfosulfuron.
2. Formation of calculi in urinary bladder	Causal	Strong	High	Accretion of crystals results in the formation of calculi (stones) in the urinary bladder. Calculi were composed primarily of the parent compound and were found in animals that developed inflammatory and irritative lesions, mucosal hyperplasia (increased cell proliferation), and tumors in the urinary bladder
3. Mucosal irritation and inflammation	Associative	Strong	High	When calculi form in the urinary bladder; the abrasive action of the calculus damages the epithelial surface causing an irritative and inflammatory reaction
4. Mucosal epithelial hyperplasia (cell proliferation)  Ulceration	Associative	Strong	Low	A hyperplastic response in the bladder occurs in the same animals that develop urinary bladder calculi and neoplastic lesions.  Evidence of ulceration in the mouse carcinogenicity study shows that penetration is occurring below the epithelia (in the submucosa) for the mesenchymal tumors

***Key event: Formation of Urinary Bladder Crystals***

The formation of urinary bladder crystals is the initiating event leading to the development of urinary bladder tumors in animals administered sulfosulfuron. Crystals were found in the urine of animals administered sulfosulfuron for 4 weeks to 22 months. In rats administered 0, 50, 500, 5000, or 20,000 ppm sulfosulfuron in the diet for 10 weeks with interim evaluations at 4 and 8 weeks, crystals were observed in urine examined by light microscopy and scanning electron microscopy (SEM) and analyzed by dispersive x-ray analysis (MRID 45643601). The results from this study, while of limited value, are summarized in Table 8. Light microscopic examination of urine showed a dose-related increase in the incidence of rats with small round crystals in urine at 5000 and 20,000 ppm and similar results were obtained when urine particulates were examined by scanning electron microscopy (SEM) and analyzed by dispersive x-ray spectroscopy at 4 and 8 weeks. There was no clear increase in the incidence or severity of crystal formation when week 4 results were compared with week 8 results. Crystals were not observed in urine of rats administered ammonium chloride (acidified the urine) in feed along

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with 5000 ppm of sulfosulfuron for 10 weeks. In addition, no crystals were found in urine of rats taken off dietary sulfosulfuron for 10 weeks in a recovery study. The recovery study showed that crystal formation is reversible. Crystals were not observed in rats fed diets containing 500 ppm or less, thus indicating the threshold nature of crystal formation.

Urine was not examined in rats fed sulfosulfuron in the diet at concentrations up to 20,000 ppm for 3 months (Table 9) (MRID 44295750). Table 10 summarizes crystal formations found in urine of rats administered sulfosulfuron in feed at concentrations of 50 to 20,000 ppm for up to 22 months in the chronic toxicity/carcinogenicity study (MRID 44295759). Because of excessive toxicity and early mortality, surviving 20,000-ppm group male rats were sacrificed on day 259 of the study. Crystals were found in the urine of ten male and nine female rats as early as 6 months at 5000 ppm and in eight males and seven females at 20,000 ppm. It is doubtful that the crystals found in two 500-ppm males at 12 months were related to sulfosulfuron administration since there was no increase in the number of animals affected at study termination and four controls also had crystals. The number of males at 5000 ppm and females at 5000 and 20,000 ppm that had crystals changed very little with continued treatment from 6 months to study termination at 22 months.

Urine was not collected in the mouse carcinogenicity study; therefore, crystal formation was not evaluated.

In a subchronic study in dogs, unidentified abnormal crystals were found in urine on day 45 and at study termination (3 months) in animals administered 300 or 1000 mg/kg bw/day of sulfosulfuron in gelatin capsules but not in animals administered 0, 30, or 100 mg/kg bw/day (Table 11) (MRID 44295751). The unidentified abnormal crystals were not found in control animals. The crystals were found in the urine on day 45 in one male and three females administered 300 mg/kg/day and two males and two females administered 1000 mg/kg/day. At study termination, crystals were found in three females at 300 mg/kg/day and four females at 1000 mg/kg/day, but in none of the male dogs. In the chronic dog study, one male and one female dog administered 500 mg/kg bw/day and one female administered 20 mg/kg/day had urinary crystals at the 6-month interim evaluation (Table 12). The lack of a clear dose-response relationship suggests that crystals in urine of female dogs were not treatment related. No treatment-related urinary crystals were found at study termination at 12 months (MRID 44295754).

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<b>TABLE 8. Crystal and calculi formation in urine and epithelial hyperplasia in the urinary bladder of male rats in a 10-week study</b>						
Crystal formation <sup>a</sup>	Dietary concentration (ppm)					
	0	50	500	5000	20,000	5000 + NH <sub>4</sub> Cl
Week 4: light microscopy (small round crystals)						
None	14 (100%) <sup>b</sup>	7	8	6 (60%)	1	9 (90%)
Few	0	1	1	0	0	1 (10%)
+1 to +5	0	0	0	4 (30%)	17	0
Week 4: x-ray analysis (spectrum of sulfur and potassium)						
None	15	7	9	0	0	5
Light & heavy	0	0	0	5	16	0
Week 8: light microscopy (small round crystals)						
None	16 (100%)	10 (100%)	10 (100%)	6 (60%)	0	9 (100%)
Few	0	0	0	1 (10%)	0	0
+1 to +5	0	0	0	3 (30%)	16 100%	0
Week 8: x-ray analysis (spectrum of sulfur and potassium)						
None	10	6	7	0	0	8
Light & Heavy	0	0	0	8	17	0
Week 10: End of treatment period						
SEM classification bladder epit. 1: flat, polygonal & 2: occasional small necrotic foci	10 (100%)	7 (70%)	9 (90%)	8 (80%)	8 (100%)	9 (90%)
3: numerous small necrotic foci & 4: extensive necrosis	0	3 (30%)	1 (10%)	2 (20%)	0	1 (10%)
Gross examination Calculi found	0	0	0	0	1	0
Microscopic examination Papillary/nodular hyperplasia of bladder epithelium	0	0	0	0	1	0
Week 21: End of recovery period						
SEM classification bladder epit. 1: flat, polygonal & 2: occasional small necrotic foci	9 (90%)	— <sup>b</sup>	—	—	2	—
3: numerous small necrotic foci & 4: extensive necrosis	1 (10%)	—	—	—	7	—

Data taken from MRID 45643601

<sup>a</sup>Grade +1: few crystals; +2: crystals present in every low power field; +3: numerous crystals, but not on entire slide; +4: crystals nearly cover slide

<sup>b</sup>No animals affected; number in parentheses is the percent of the number of animals examined.

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<b>TABLE 9. Crystal and calculi formation in urine and epithelial hyperplasia in the urinary bladder of rats in the subchronic toxicity study</b>						
	Dietary concentration					
	0	20	200	2000	6000	20,000
<b>Males</b>						
Crystals	Urine was not examined					
Calculi	0/10	0/10	0/10	0/10	0/10	1/10
Mucosal epithelial hyperplasia	0/10	Not examined	Not examined	Not examined	Not examined	1/10
<b>Females</b>						
Crystals	Urine was not examined					
Calculi	0/10	0/10	0/10	0/10	0/10	0/10
Mucosal epithelial hyperplasia	0/10	Not examined	Not examined	Not examined	Not examined	1/10

Data taken from Data Evaluation Record, MRID 44295750.

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<b>TABLE 10. Crystal and calculus formation in urine and epithelial hyperplasia in the urinary bladder of rats in the chronic toxicity/carcinogenicity feeding study</b>					
<b>Dietary concentration (ppm)</b>					
	<b>0</b>	<b>50</b>	<b>500</b>	<b>5000</b>	<b>20,000<sup>b</sup></b>
<b>Crystals (examination of urine)</b>					
Males: 6 months	0 <sup>a</sup>	0	0	10	8
Males: 12 months	0	0	2	10	—
Males: 18 months	0	1	0	7	—
Males: 22 months	4	4	2	8	—
Females: 6 months	1	2	2	9	7
Females: 12 months	0	0	0	7	8
Females: 18 months	0	1	1	7	9
Females: 22 months	1	0	2	8	10
<b>Calculus (found at necropsy)</b>					
Males: 12 month interim sac.	0/10	1/10	0/10	0/10	—
Males: main study <sup>c</sup>	2/50	1/50	0/50	2/50	29/60
Females: 12 month interim sac.	0/10	0/10	0/10	1/10	1/10
Females: main study <sup>c</sup>	0/50	0/50	0/50	2/50	5/50
<b>Epithelial hyperplasia (microscopic examination)</b>					
Males: 12 month interim sac.	0/10	1/10	0/10	0/10	—
Males: main study <sup>c</sup>	6/46	5/49	5/49	9/50	14/21 <sup>d</sup>
Females: 12 month interim sac.	0/10	0/10	0/10	1/10	3/10
Females: main study <sup>c</sup>	2/50	2/50	0/50	2/50	7/50
<b>Neoplastic lesions: Urinary Bladder</b>					
<b>Males</b>					
Transitional cell papilloma	0/56	0/59	0/59	0/60	0/21
Transitional cell carcinoma	0/56	0/59	0/59	0/60	0/21
<b>Females</b>					
Transitional cell papilloma	0/60	0/59	0/60	1/60	0/57
Transitional cell carcinoma	0/60	0/59	0/60	1/60	0/57
Data taken from MRID 45362801 and 44295759 (Data Evaluation Record)					
<sup>a</sup> Number of animals affected					
<sup>b</sup> All surviving males sacrificed on day 259 of the study; none alive at interim sacrifice.					
<sup>c</sup> Unscheduled and scheduled deaths					
<sup>d</sup> The study authors (MRID 45362801) and Data Evaluation Record (MRID 44295759) did not explain why only 21 animals were examined microscopically.					

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**TABLE 11. Crystal and calculus formation in urine and epithelial hyperplasia in the urinary bladder of dogs in a 90-day subchronic toxicity study**

Parameter	Dose (mg/kg bw/day)				
	0	30	100	300	1000
Crystals (urine)					
Males: 45 day evaluation	0	0	0	1	2
Females: 45 day evaluation	0	0	0	3	2
Males: 90-day (termination)	No crystals at any dose				
Females: 90-day (termination)	0	0	0	3	4
Calculus (necropsy)					
Males	None reported at these doses				1 (urolithiasis)
Females	None reported at any dose				
Histopathology (urinary bladder mucosa)					
Males: multiple lesions (hemorrhage, erosions, ulcerations, acute inflammation, and degeneration of tunica muscularis, or edema)	0	0	0	0	2 <sup>a</sup>
Females: multiple lesions (hemorrhage, , ulcerations, and acute inflammation, or mucosal epithelial hyperplasia)	0	0	0	1 <sup>b</sup>	1

Data taken from MRID 44295751 (Data Evaluation Record)

<sup>a</sup>One male had all lesions except edema (also had urolithiasis; killed *in extremis* on day 75; the other male had all lesions except degeneration of tunica muscularis.<sup>b</sup>Mucosal epithelial hyperplasia was not observed at 300 mg/kg/day.**TABLE 12. Crystal and calculus formation in urine and epithelial hyperplasia in the urinary bladder of dogs in a 1-year chronic toxicity study**

Parameter	Dose (mg/kg bw/day)				
	0	5	20	100	500
Crystals (urine)					
Males: 6-month evaluation	0	0	0	0	1
Females: 6-month evaluation	0	0	1	0	1
Males: 1-year (termination)	No crystals at any dose				
Females:1-year (termination)	No crystals at any dose				
Calculus (necropsy at 1 year)					
Males	None reported at these doses				1
Females	None reported at any dose				
Histopathology (urinary bladder mucosa) at 1 year					
Males: hemorrhage and edema	0	0	0	0	1
Females:	0	0	0	0	0

Data taken from MRID 44295754 (Data Evaluation Record)

<sup>a</sup>One male did not have edema s and the other male did not have degeneration of tunica muscularis.<sup>b</sup>Mucosal epithelial hyperplasia was not observed at 300 mg/kg/day.

***Key event: Formation of Urinary Bladder Calculi***

In the 10-week study in male rats, urinary bladder calculi were found at necropsy in only one rat fed the 20,000-ppm diet (MRID 45643601) (see Table 8). No calculi were found in the controls or animals fed lower dietary concentrations of sulfosulfuron. [Note: The CARC concluded that this study was not very useful. This study was performed using male rats but tumors were found in female rats; calculi and hyperplasia were observed in only 1 animal at 20,000 ppm; no calculi/hyperplasia were observed at 5000 ppm (the dose at which tumors were observed).] In the 13-week subchronic rat study, calculi also were found in the urinary bladder during necropsy of one male rat treated with sulfosulfuron at 20,000 ppm, but not at lower concentrations in males or at any dietary concentration in females (Table 9) (MRID 44295750).

In a chronic/carcinogenicity rat study (MRID 44295759), the incidence of urinary bladder calculi was very high in 20,000-ppm males; these animals suffered from severe urolithiasis (stones) and associated toxicity that caused early mortality (Table 10). Almost one-half the 20,000-ppm group males had calculi when the remaining surviving animals were sacrificed on day 259. No treatment-related calculi were found in males in the 50-, 500-, or 5000-ppm groups maintained until sacrifice at 22 months. Only 10% of females in the 20,000-ppm group and 4% in the 5000-ppm group had urinary bladder calculi compared with none of the controls and 50- and 500-ppm groups. In a separate study (MRID 45079602), calculi were collected from two rats in the 20,000-ppm group and one in the 5000-ppm group for analysis of sulfosulfuron content. Calculi collected from the 20,000-ppm rats contained 94.1% and 101.6% sulfosulfuron, whereas calculi collected from the 5000-ppm rat contained 70.9% sulfosulfuron. This analysis showed that calculi consist almost entirely of unmetabolized test material.

In a carcinogenicity study, mice were fed sulfosulfuron in the diet at 0, 30, 700, 3000 or 7000 ppm for 18 months (MRID 44295755). Gross examination showed calculi in the urinary bladder in 35% and 68% of male mice at 3000 and 7000 ppm, respectively (Table 13). Bladder calculi/microcalculi were observed microscopically in the bladder of male mice at 3000 and 7000 ppm, but at a much lower incidence than observed grossly. Calculi were observed during necropsy in the urinary bladder of only one female mouse at 7000 ppm and in none when examined microscopically.

In a subchronic study, one male dog administered sulfosulfuron at 1000 mg/kg/day for 3 months had calculi at several sites in the urinary tract and was sacrificed early because of complications due to urolithiasis (urinary tract stones or calculi) (MRID 44295751) (Table 11). Although crystals were found in the urine of other dogs administered sulfosulfuron at 300 and 1000 mg/kg/day for 45 days and 3 months, calculi were not found in these animals at necropsy. Lesions in the bladder consistent with the presence of calculi were observed in another male dog at 1000 mg/kg/day and one female each at 300 and 1000 mg/kg/day after treatment for 3 months. In the chronic study, a male dog that had urinary crystals after administration of sulfosulfuron at 500 mg/kg/day for 6 months had calculi in the urinary tract with continued treatment for 1 year (MRID 44295754) (Table 12). Calculus formation was not observed in other dogs administered sulfosulfuron for 1 year.

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<b>TABLE 13 Crystal and calculus formation in urine and epithelial hyperplasia in the urinary bladder of mice in the carcinogenicity feeding study</b>					
<b>Parameter examined</b>	<b>Dietary concentration (ppm)</b>				
	<b>0</b>	<b>30</b>	<b>700</b>	<b>3000</b>	<b>7000</b>
<b>Calculus (found at necropsy)</b>					
Males: interim sac. & main study	1 <sup>a</sup>	0	0	21 (35%)	41 (68%)
Females: interim sac. & main study	0	0	0	0	1
<b>Calculus/microcalculus (microscopic examination)</b>					
Males: interim sac. & main study	1/59	0/59	0/59	4/59 (7%)	10/60** (17%)
Females: interim sac. & main study	0	0	0	0	0
<b>Mucosal Epithelial Hyperplasia (microscopic examination)</b>					
Males: interim sac. & main study	4/59	1/59	2/59	25/59** (42%)	41/60** (68%)
Females: interim sac. & main study	0/50	0/10	0/56	0/58	1/58
<b>Other Urinary Bladder Lesions (microscopic examination) - Males</b>					
Dilatation	5/59	4/59	3/59	8/59	20/60** (33%)
Chronic inflammation	2/59	3/59	2/59	23/59** (39%)	41/60** (68%)
Squamous metaplasia	0/59	0/59	0/59	1/59	8/60** (13%)
Ulceration	0/59	1/59	0/59	3/59	4/59
<b>Neoplastic Lesions in Urinary Bladder</b>					
<b>Mesenchymal tumors –</b>					
Males	0/45	0/46	0/48	1/47	5/44

Data taken from MRID 44295755 (Data Evaluation Record)

<sup>a</sup>Number of animals affected; n = 60 unless otherwise noted.

\*\*p&lt;0.01, compared with controls.

***Key event: irritation and inflammatory lesions in the urinary bladder***

No treatment-related increase in the incidence of lesions indicative of irritation or inflammation was observed in the urinary bladder of rats fed sulfosulfuron for up to 22 months, including the 20,000-ppm group males sacrificed early because of severe urolithiasis (see Table 10). In the mouse carcinogenicity study, the incidences of urinary bladder dilatation, chronic inflammation, and squamous metaplasia were significantly increased in males at 7000 ppm and the incidence of chronic inflammation was significantly increased in males at 3000 ppm (Table 13). The incidence of ulceration in the urinary bladder was increased (not s.s.) in males at 3000 ppm (3/59, 5%) and 7000 ppm (4/59, 7%). Urinary bladder irritation and inflammation are often found in animals that have developed calculi (Cohen et al., 2002).

In the subchronic dog study, urinary bladder hemorrhage, erosion, ulceration with acute inflammation, and degeneration of the tunica muscularis were observed in one male animal sacrificed early because of severe urolithiasis and complications (Table 11). Similar lesions were found in the urinary bladder of another male dog at 1000 mg/kg/day, one female at 1000 mg/kg/day and one female at 300 mg/kg/day (acute inflammation, erosion, ulceration, and edema) in the absence of visible calculi. Hemorrhage and edema were observed in the urinary bladder of one male dog administered sulfosulfuron at 1000 mg/kg/day for 1 year (Table 12).

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***Key event: Epithelial Hyperplasia in the Urinary Bladder (mucosal epithelial hyperplasia, urothelial hyperplasia)***

In a 10-week study using male rats (MRID 45643601), papillary/nodular epithelial hyperplasia of the urinary bladder was observed in one rat (male) in the 20,000-ppm group (Table 8). One male and one female rat in the 20,000-ppm group in the 13-week subchronic study also had mucosal epithelial hyperplasia (Table 9) (MRID 44295750).

In the chronic/carcinogenicity study in rats (MRID 44295759), no males in the 20,000-ppm group were alive at 12 months for interim evaluation. The incidence of epithelial hyperplasia of the urinary bladder in males was 18% (9/50) at 5000 ppm (terminated at 22 months) and 67% (14/21 rats) at 20,000 ppm males (terminated at day 259) compared with 13% (6/46) in controls (Table 10). In females, the incidence was 10% (1/10) at 5000 ppm, 30% (3/10) at 20,000 ppm, and 0% (0/10) in controls at 12 months. In the main study terminated at 22 months, there was an increase (not statistically significant) in the incidence of epithelial hyperplasia 20,000-ppm (14%, 7/50) females compared with 4% (2/50) in the control group.

In the mouse carcinogenicity study (MRID 44295755), mucosal epithelial hyperplasia of the urinary bladder was observed in 42% and 68% (statistically significant at  $p < 0.01$ ) of male mice fed the 3000- and 7000-ppm diets, respectively (Table 13). Epithelial hyperplasia was observed in the urinary bladder of only 2% (1/58) of female mice fed the 7000-ppm diet.

In dogs, mucosal epithelial hyperplasia was observed in the urinary bladder of one female dog administered 1000 mg/kg bw/day for 13 weeks and in none of the males (Table 11) (MRID 44295751). In the chronic study, hyperplasia in the urinary bladder was not observed in dogs administered sulfosulfuron at doses up to 500 mg/kg bw/day for 12 months (Table 12) (MRID 44295754).

***Key Event: Neoplastic Lesions in the Urinary Bladder***

In rats administered sulfosulfuron in the diet for up to 22 months, one female rat administered the 5000-ppm diet developed a transitional cell papilloma and another female developed a transitional cell carcinoma (Table 10). Urinary bladder neoplasms did not develop in female rats administered the 20,000-ppm diet nor in males administered any dose. The 20,000-ppm male group was terminated early because of excessive toxicity and mortality; therefore, no animals were alive for evaluating late-developing neoplastic lesions.

In the mouse carcinogenicity study, submucosal mesenchymal tumors were observed in the urinary bladder of five male mice administered the 7000-ppm diet, one male mouse administered the 3000-ppm diet, but none of the controls (Table 13) (MRID 44295755). In addition, submucosal mesenchymal tumors were observed in the urinary bladder of one female mouse administered the 7000-ppm diet and one female control. The male mice that had submucosal mesenchymal tumors also had grossly visible calculi, transient cell hyperplasia (not otherwise described), and inflammation. An explanation for the development of submucosal mesenchymal tumors involved the separation of layers of muscle cells, repopulation of the space between the

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layers with mesenchymal cells, induction of irritation, inflammation, and obstruction by calculi, and release of cytokines leading to proliferation of the mesenchymal cells (MRID 45362801). The development of submucosal mesenchymal tumors was correlated with urinary bladder calculi.

***Summary and Time Line of Key Events in the Proposed Mode of Action***

The temporal sequence of key events in the mode of action for induction of urinary bladder tumors in sulfosulfuron-treated animals is presented in Table 14. The formation of crystals in the urine appears to be the earliest event in the mode of action. Crystals were present in rat urine after administration of sulfosulfuron for only 4 weeks and in dog urine after dosing for about 6 weeks. The earliest time at which crystals are formed after initiation of treatment is not known because no studies were available for time points less than 4 weeks. The earliest time during administration of sulfosulfuron at which animals were sacrificed and examined grossly for calculi in the urinary bladder was 10 weeks. Calculi were found in the urine of one male rat administered the highest dietary concentration (20,000 ppm) but in none of the females. Papillary/nodular epithelial hyperplasia in the urinary bladder also was observed in the same animal sacrificed after treatment for 10 weeks. Calculi and epithelial hyperplasia also were observed after treatment of rats and dogs for 13 weeks, after treatment of rats for 12 months, and after treatment of mice and rats for 18 to 22 months. Although calculi were found in one male dog after treatment for 12 months, and injury to the bladder epithelium was evidenced by hemorrhage and edema, epithelial hyperplasia was not observed. Transitional cell papilloma and carcinoma were observed at 5000 ppm in female rats. Crystals, calculi, and mucosal epithelial hyperplasia were observed in the groups of female rats that developed transitional cell neoplasms. Submucosal mesenchymal tumors were observed in male mice at the highest dose. The mice that had submucosal mesenchymal tumors also had calculi in the urinary bladder. The data showed dose-related increases in the incidences of urinary bladder calculi and non-proliferative lesions (dilatation, chronic inflammation, and ulceration).

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<b>TABLE 14. Temporal sequence of key events in animals administered sulfosulfuron</b>	
<b>Species</b>	<b>Event</b>
<b>4 Weeks</b>	
Rat	Crystals in urine (males)
<b>45 Days (~6 Weeks)</b>	
Dog	Crystals in urine (males & females)
<b>8 Weeks</b>	
Rat	Crystals in urine (males)
<b>10 Weeks</b>	
Rat	Calculi found during necropsy (males) Papillary/nodular hyperplasia of bladder epithelium found during microscopic examination (males)
<b>90 Days (13 Weeks)</b>	
Rat	Urine not examined for crystals (males & females) Calculi found during necropsy (male only) Mucosal epithelial hyperplasia (male & female)
Dog	Calculi (urolithiasis) (male) Multiple non-proliferative lesions in urinary bladder mucosa (hemorrhage, erosion, ulceration, inflammation, degeneration of tunica muscularis, edema) (males and females) Mucosal epithelial hyperplasia (female only)
<b>6 Months</b>	
Rat	Crystals in urine (males & females)
Dog	Crystals in urine (male & female)
<b>12 Months</b>	
Rat <sup>a</sup>	Crystals in urine (males & females) Calculus (males) Mucosal epithelial hyperplasia (males & females)
Dog	No crystals found (males & females) Calculus (male) Hemorrhage and edema in bladder mucosa (male)
<b>18-22 Months</b>	
Mouse <sup>b</sup>	Calculi (males) Non-proliferative lesions (dilatation, chronic inflammation, ulceration, squamous metaplasia) (males) Mucosal epithelial hyperplasia (males) Mesenchymal tumors (males)
Rat <sup>a</sup>	Crystals in urine (females) Calculus (females) Mucosal epithelial hyperplasia (females) Transitional papilloma/carcinoma (females)

<sup>a</sup>High dose males terminated on day 259<sup>b</sup>Data for interim and 18-month study were combined.

***Relevance of submucosal mesenchymal tumors in the urinary bladder***

Mesenchymal neoplasms observed in the urinary bladder of humans include leiomyosarcomas, the most common malignant type in adult humans, and rhabdomyosarcoma, the most common type found in children. Leiomyoma is a benign mesenchymal bladder tumor found in the urinary bladder of humans; this tumor has very low mitotic activity and minimal cellular atypia (Lott et al., 2007). In the past, lesions similar to submucosal mesenchymal tumors in mice were diagnosed as leiomyomas, leiomyosarcomas, sarcomas, hemangiomas, or hemangiosarcomas (Gaillard, 1999), suggesting a similarity among these lesions. Because of the similarity of the mesenchymal lesions in animals and humans, submucosal mesenchymal lesions are considered relevant to humans.

***Alternative MOAs***

No data were found to support alternative modes of action, including oxidative stress or cytotoxicity. Also, sulfosulfuron is not mutagenic.

***Conclusions***

The evidence has shown that treatment with sulfosulfuron leads to crystal formation in urine. The crystals then accrete to form calculi in the urinary bladder, and the abrasive action of calculi in the bladder epithelium causes irritative (erosion and ulceration) and inflammatory lesions in the urinary bladder. Destruction of the mucosal epithelium leads to a regenerative (cell proliferation) response and epithelial hyperplasia. Calculi found in the urinary bladder are made up primarily of unmetabolized parent compound, sulfosulfuron. Transitional cell neoplasms are generally associated with calculi and epithelial hyperplasia in the urinary bladder. Transitional cell neoplasms were found in two female rats administered the 5000-ppm diet but not in females administered the 20,000-ppm diet. The incidence of urinary bladder calculi, which are considered a prerequisite for development of transitional cell neoplasms, showed a clear dose-response relationship. In addition, epithelial hyperplasia was observed at 5000 ppm, at 12 months. Therefore, this evidence suggests that the transitional cell neoplasms in female rats are related to treatment with sulfosulfuron.

The development of submucosal mesenchymal tumors in male mice was associated with the presence of calculi. Male mice that developed submucosal mesenchymal tumors also had urinary bladder calculi. Treatment-related submucosal mesenchymal tumors were not observed in female mice. In addition to the neoplasms, urinary bladder dilatation, chronic inflammation, and ulceration were observed in male mice also but not in female mice.

The evidence showed that the development of urinary bladder tumors is a high-dose threshold phenomenon. Calculi and urinary bladder tumors were found only in animals administered high doses. If the dose was too low to produce calculi, urinary bladder tumors did not develop. Therefore, the evidence supports a non-linear (threshold) mode of action with development of calculi being a prerequisite for development of urinary bladder tumors in sulfosulfuron-treated animals. These tumors are considered to be relevant to humans.

## V. COMMITTEE'S ASSESSMENT OF WEIGHT-OF-EVIDENCE

The Committee considered the following for a weight-of-evidence determination on the carcinogenic potential of sulfosulfuron:

### 1. Carcinogenicity

#### Rats

- Urinary Bladder Tumors:* At 5,000 ppm, a urinary bladder transitional cell papilloma and carcinoma were each observed in one female rat (2 different animals, each 1 out of 60 animals; not statistically significant). These tumors were not observed in females at lower doses or at the highest dose tested (HDT) of 20,000 ppm, nor in male rats at any dose level. The incidence of papilloma at 5000 ppm (2%) was within the historical control range of the testing laboratory, however the incidence of carcinoma at 5000 ppm was outside the historical control value (0%). The animals that had transitional cell tumors also had calculus formation and related urinary bladder pathology (epithelial hyperplasia). In spite of the lack of dose-response and the low incidence, the CARC concurred with the previous CARC's decision that these bladder tumors are treatment-related since this is a rare tumor, the urinary tract is the target organ, and precursor lesions for the MOA for urinary bladder tumors were noted.
- Adequacy of Dosing:* In males, 5000 ppm was considered to be adequate for assessing the carcinogenic potential of sulfosulfuron based on the abnormal crystals in the urine and slightly increased incidences of kidney and urinary bladder calculi and related lesions (dilatation of the renal pelvis and bladder, urinary bladder epithelial hyperplasia) as well as the increased incidence of mineralization of the heart, lung, pancreas and skeletal muscle. The intended high dose of 20,000 ppm, discontinued at day 259, was considered excessive due to high mortality secondary to urolithiasis-related pathology.

In females, dosing at 5000 ppm was considered adequate for assessing the carcinogenic potential of sulfosulfuron. At 5000 ppm (high-mid dose), increased incidences of abnormal urinary crystals, and slightly increased incidences of renal pelvic epithelial hyperplasia and gastric pyloric lesions were observed. The incidence of grossly visible calculi was also increased. At 20,000 ppm (highest dose tested), toxicity to the urinary tract was pronounced. Slightly increased mortality, decreased body weight/weight gain, emaciated appearance, slightly increased BUN, systemic mineralization, fibrous osteodystrophy of the femur and sternum and parathyroid hyperplasia were also observed. Some Committee members considered this dose excessive because mineralization in many organs, may have compromised normal physiological function.

#### Mouse

- Urinary Bladder Tumors:* The incidences of benign mesenchymal tumors of the urinary bladder in male mice for average daily doses of 0, 30, 700, 3000, and 7000 ppm,

respectively, were:

Benign 0/45, 0/46, 0/48, 1/47 (2%), 5/44 (11%)

There was a significant increasing trend (at  $p < 0.01$ ) and a significant difference in the pair-wise comparison of the high dose group compared to the control (at  $p < 0.05$ ) for benign mesenchymal tumors of the urinary bladder. The incidence at the high dose (11%) also exceeded the historical control data from the testing lab (0-2%). The CARC concurred with the 1998 CARC decision that these tumors were treatment-related since they exceeded the concurrent control and historical control data from the testing laboratory, the urinary tract was the primary target organ of sulfosulfuron, and precursor lesions for the MOA for urinary bladder tumors were noted.

- *Kidney Tumors:* Kidney tubule adenomas were found in one male and one female mouse administered the highest concentration of sulfosulfuron in the diet (7000 ppm). A re-evaluation of the histopathology findings from the chronic mouse study was performed by Dr. Gordon Hard, an international expert in the field of mouse kidney tumors. It was concluded that the renal tubules failed to show any evidence of treatment-related cellular injury or death, increased mitotic activity, or increased nuclear size. Also, there was no incidence of compound-induced hyperplasia. Chronic progressive nephropathy (CPN) was observed with almost 100% occurrence in the four treatment groups, including controls. The severity of these lesions was comparable among groups. Therefore, this evaluation indicates that the kidney adenomas were not treatment-related.
- *Adequacy of Dosing:* The highest dose tested (7000 ppm) was considered adequate for assessing the carcinogenic potential of sulfosulfuron. In males, urinary tract pathology secondary to treatment-related urolithiasis were observed at 3000 and 7000 ppm and included mucosal epithelial hyperplasia, chronic inflammation and ulceration. Although no treatment-related toxicity was seen in females at this dose (7000 ppm), since it is the limit-dose for carcinogenicity testing, dosing was considered to be adequate for assessing carcinogenicity.

## 2. Mutagenicity

- There is no concern for mutagenicity.

## 3. Structure Activity Relationship

- Sulfosulfuron is a sulfonylurea herbicide and is structurally related to several other sulfonylurea compounds. As a group, these compounds do not show evidence of carcinogenicity among those that have been classified. Some sulfonamide drugs which are carbonic anhydrase inhibitors have been shown to cause urinary calculus formation and bladder tumors in rodents.

A Derek Analysis was also performed for sulfosulfuron. The Derek analysis for sulfosulfuron reported an alert for bladder urothelial hyperplasia based on the aryl sulphonamide portion of the parent structure. The toxicophore for this alert has been

based on the chemical structures of well-known sulphonamide-type carbonic anhydrase inhibitors and some consideration of potential precursors (hydrolysis of N-acetyl groups to the free amine). In addition to the aryl sulphonamide alert, a carcinogenic alert was reported based on the bladder urothelial hyperplasia being associated with the formation of tumors of the bladder. This alert is based on the substituted pyrimidine or purine structure. Pyrimidine derivatives have been shown to have carcinogenic potential include uracil and thymine, which included bladder carcinogenesis in rats and/or mice via calculi formation. Urinary calculi are formed when the urine becomes oversaturated with a compound. Large calculi then damage the urinary bladder epithelium mechanically and increase DNA synthesis in the cells resulting in tumor formation. In conclusion, these structural alerts correspond accurately with the results of the empirical data for potential bladder carcinogenicity based on a non-genotoxic mode of action based on a high dose phenomenon that includes formation of urinary calculi causing damage to the urinary bladder epithelium which increases cellular proliferation and hyperplasia which lead to bladder tumor formation.

#### 4. Mode of Action

- The series of events leading to urinary bladder tumors (mesenchymal and transitional cell) are initiated by the formation of crystals in urine and the aggregation (accretion) of crystals to form calculi or stones, which induce a hyperplastic (preneoplastic) response in the urinary bladder epithelium. Urinary bladder epithelial hyperplasia is a regenerative response resulting from irritation and inflammation caused by an abrasive action of calculi on the urinary bladder epithelium. Urinary bladder lesions that precede or accompany epithelial hyperplasia may include inflammation (acute or chronic), ulceration, and necrosis. Crystal formation in the absence of calculi is not associated with hyperplasia or urinary bladder tumors; therefore, the formation of urinary bladder calculi is the prerequisite for subsequent hyperplasia and neoplasia. The requirement for calculi formation also supports high-dose threshold phenomenon for the development of urinary bladder tumors, i.e., tumors do not develop at doses too low to produce calculi.

## VI. Classification of Carcinogenic Potential

In accordance with EPA's *Final Guidelines for Carcinogen Risk Assessment (March 2005)*, the CARC classified Sulfosulfuron as "Not Likely to be Carcinogenic to Humans" at doses that do not cause crystals with subsequent calculi formation resulting in cellular damage of the urinary tract. This classification was based on urinary bladder tumors seen in female rats and male mice. Crystal formation in the absence of calculi is not associated with hyperplasia or urinary bladder tumors; therefore, the formation of urinary bladder calculi is the prerequisite for subsequent hyperplasia and neoplasia. The requirement for calculi formation also supports a high-dose threshold phenomenon for the development of urinary bladder tumors, i.e., tumors do not develop at doses too low to produce calculi. There is no concern for mutagenicity.

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**VII. Quantification of Carcinogenic Potential**

A quantified approach to cancer risk assessment is not required.

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